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Description

This invention was made with United States government support awarded by the Department of Health and Human Services (NIH), Grant number: DK-14881. The United States Government has certain rights in this invention.

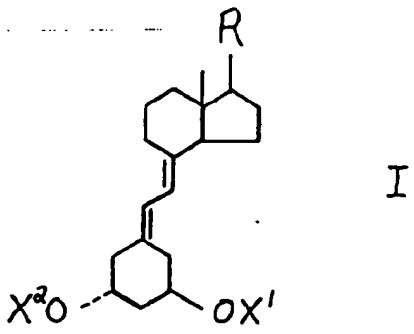
This invention relates to biologically active vitamin D compounds. More specifically, the invention relates to 19-nor-analogs of 1α-hydroxylated vitamin D compounds and to a general process for their preparation.

Background

The 1α-hydroxylated metabolites of vitamin D – most importantly 1α ,25-dihydroxyvitamin D_3 (See US-A-3697559) and 1α,25-dihydroxyvitamin D_2 – are known as highly potent regulators of calcium homeostasis in animals and hunans, and more recently their activity in cellular differentiation has also been established. As a consequence, many structural analogs of these metabolites, such as compounds with different side chain structures, different hydroxylation patterns, or different stereochemistry, have been prepared and tested. Important examples of such analogs are 1α -hydroxyvitamin D_3, 1α-hydroxyvitamin D_2, various side chain fluorinated derivatives of 1α,25-dihydroxyvitamin D_3, and side chain homologated analogs. Several of these known compounds exhibit highly potent activity in vito or in vitro, and possess advantageous activity profiles and thus are in use, or have been proposed for use, in the treatment of a variety of diseases such as renal osteocystrophy, vitamin D-resistant rickets, osteoporosis, psoriasis, and certain malignancies.

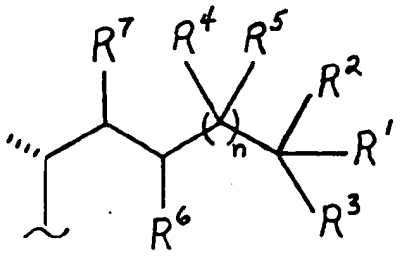
Disclosure and Description of the Invention

A class of 1α-hydroxylated vitamin D compounds not known heretofore are the 19-nor-analogs, i.e. compounds in which the ring A exocyclic methylene group (carbon 19) typical of all vitamin D system has been removed and replaced by two hydrogen atoms. Structurally these novel analogs are characterized by the general formula I shown below:



I

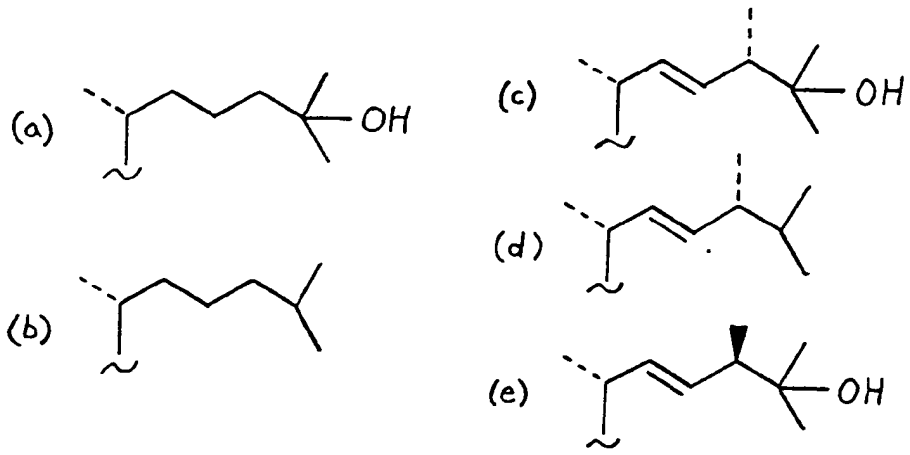
where X^1 and X^2 are each selected from the group consisting of hydrogen and acyl, and where the group R represents any of the typical side chains known for vitamin D type compounds. Thus, R may be an alkyl, hydrogen, hydroxyalkyl or fluoroalkyl group, or R may represent the following side chain:



wherein R^1 represents hydrogen, hydroxy or O-acyl, R^2 and R^3 ar each s lected from the group consisting of alkyl, hydroxyalkyl and fluoroalkyl, or, when taken together represent the group -- $(CH_2)_m$ -- wher m is an integer having a valu of from 2 to 5, R^4 is selected from the group consisting of hydrog n, hydroxy, fluorine, O-

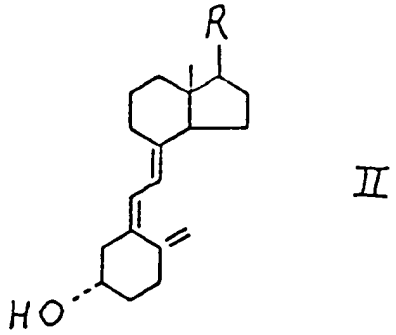
acyl, alkyl, hydroxyalkyl and fluoroalkyl, R^5 is selected from the group consisting of hydrogen, fluorin , alkyl, hydroxyalkyl and fluoroalkyl, or, R^4 and R^5 taken together represent double-bonded oxygen, R^6 and R^7 are each selected from the group consisting of hydrogen, hydroxy, O-acyl, fluorine and alkyl, or, R^6 and R^7 taken together f rm a carbon-carbon double bond, and wherein n is an integer having a value of from 1 to 5, and wherein the carb n at any one of positions 20, 22, or 23 in the side chain may be replaced by an O, S, or N atom.

Specific important examples of side chains are the structures represented by formulas (a), (b), (c), (d) and (e) below, i.e. the side chain as it occurs in 25-hydroxyvitamin D_3 (a); vitamin D_3 (b); 25-hydroxyvitamin D_2 (c); vitamin D_2 (d); and the C-24-epimer of 25-hydroxyvitamin D_2 (e).



In this specification and the claims, the term 'alkyl' signifies an alkyl radical of 1 to 5 carbons in all isomeric forms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, etc., and the terms 'hydroxyalkyl' and 'fluoroalkyl' refer to such an alkyl radical substituted by one or more hydroxy or fluoro groups respectively, and the term 'acyl' means an aliphatic acyl group of 1 to 5 carbons, such as formyl, acetyl, propionyl, etc. or an aromatic acyl group such as benzoyl, nitrobenzoyl or halobenzoyl. The term 'aryl' signifies a phenyl-, or an alkyl-, nitro- or halo-substituted phenyl group.

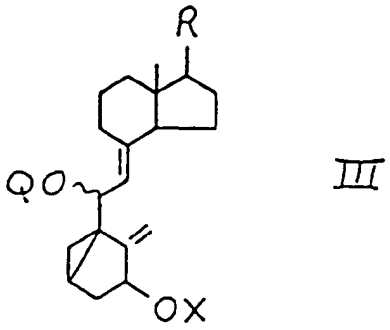
The preparation of 1α-hydroxy-19-nor-vitamin D compounds having the basic structure shown above can be accomplished by a common general method, using known vitamin D compounds as starting materials. Suitable starting materials are, for example, the vitamin D compounds of the general structure II:



II

where R is any of the side chains as defined above. These vitamin D starting materials are known compounds, or compounds that can be prepared by known methods.

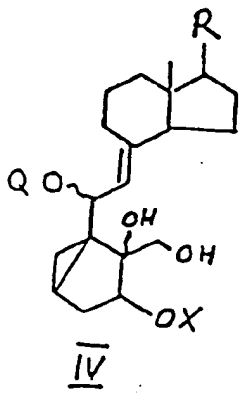
Using the procedure of DeLuca et al. (U.S. Patent 4,195,027), the starting material can be converted to the corresponding 1α-hydroxy-3,5-cyclovitamin D derivative, having the general structure III below, where X represents hydrogen and Q represents an alkyl, preferably methyl:



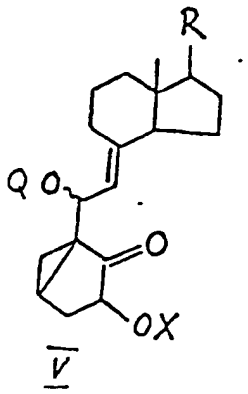
III

So as to preclude undesired reaction of the 1α-hydroxy group in subsequent steps, the hydroxy group is converted to the corresponding acyl derivative, i.e. the compound III shown above, where X represents an acyl group, using standard acylation procedures, such as treatment with an acyl anhydride or acyl halide in pyridine at room temperature or slightly elevated temperature (30-70°C). It should be understood also that whereas the process of this invention is illustrated here with acyl protection of hydroxy functions, alternative standard hydroxy-protecting groups can also be used, such as, for example, alkylsilyl or alkoxyalkyl groups. Such protecting groups are well-known in the art (e.g. trimethylsilyl, triethylsilyl, t.-butyldimethylsilyl, or tetrahydrofuranyl, methoxymethyl), and their use is considered a routine modification of experimental detail within the scope of the process of this invention.

The derivative as obtained above can then be reacted with, say osmium tetroxide, to produce the 10,19-dihydroxy analog, IV (where X is acyl), which is subjected to diol cleavage using sodium metaperiodate or similar vicinal diol cleavage reagents (e.g. lead tetraacetate) to obtain the 10-oxo-intermediate, having the structure V below (where X is acyl):



IV

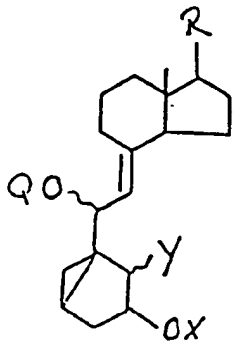


V

These two consecutive steps can be carried out according to the procedures given by Paaren et al. [J. Org. Chem. 48, 3819 (1983)]. If the side chain unit, R, carries vicinal diols (e.g. 24,25-dihydroxy- or 25,26-dihydroxy, etc.), these, of course, also need to be protected, e.g. via acylation, silylation, or as the isopropylidene derivative prior to the periodate cleavage reactions.

In most cases, the acylation of the 1α-hydroxy group as mentioned above will simultaneously effect the acylation of side chain hydroxy functions, and these acylation conditions can, of course, be appropriately adjusted (e.g. elevated temperatures, longer reaction times) so as to assure complete protection of side chain vicinal diol groupings.

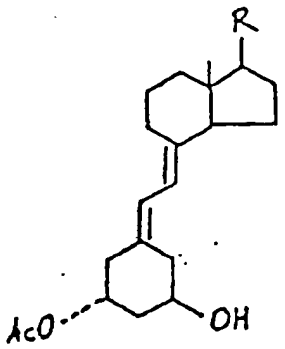
The next step of the process comprises the reduction of the 10-oxo-group to the corresponding 10-alcohol having the structur VI shown below (where X is acyl and Y represents hydroxy). When X is acyl, this reduction is carried out conveniently in an organic solvent at from, say, 0°C to room temp rature, using $NaBH_4$ or equivalent hydride reducing agents, selective for the reduction of carbonyl groups without cleaving ester functions. Obviously, when X is a hydroxy-protecting group that is stabl to reducing ag nts, any of the oth r hydride reducing agents (.g. $LiAlH_4$, or analogous r agents) may be employed also.



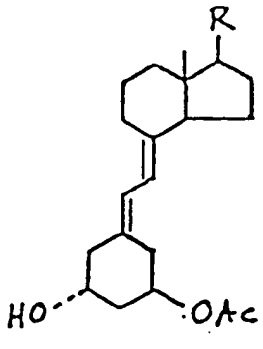
VI

The 10-hydroxy intermediate can then be treated with an alkyl- or arylsulfonylhalide (e.g. methanesulfonyl-chloride) in a suitable solvent (e.g. pyridine) to obtain the corresponding 10-O-alkyl- or arylsulfonyl derivative (the compound having the structure shown VI above, where Y is alkyl-SO_2O-, or aryl-SO_2O-, and this sulfonate intermediate is then directly reduced, e.g. with lithiun aluminum hydride, or the analogous known lithium aluminum alkyl hydride reagents in an ether solvent, at a temperature typically from 0°C to the boiling temperature of the solvent, thereby displacing the sulfonate group and obtaining the 10-deoxy derivative, represented by the structure VI above, where X and Y are both hydrogen. As shown by the above structure, a 1-O-acyl function in the precursor compound V is also cleaved in this reduction step to produce the free 1α-hydroxy function, and any O-acyl protecting group in the side chain would, of course, likewise be reduced to the corresponding free alcohol function, as is well understood in the art. If desired, the hydroxy groups at C-1 (or hydroxy groups in the side chain) can be reprotected by acylation or silylation or ether formation to the corresponding acyl, alkylsilyl or alkoxyalkyl derivative, but such protection is not required. Alternative hydroxy-protecting groups, such as alkylsilyl or alkoxyalkyl groups would be retained in this reduction step, but can be removed, as desired, at this or later stages in the process by standard methods known in the art.

The above 1α-hydroxy-10-deoxy cyclovitamin D intermediate is next solvolyzed e.g the presence of a low-molecular weight organic acid, using the conditions of DeLuca et al. (U.S. Patents 4,195,027 and 4,260,549). When the solvolysis is carried out in acetic acid, for example, there is obtained a mixture of 1α-hydroxy-19-nor-vitamin D 3-acetate and 1α-hydroxy-19-nor-vitamin D 1-acetate (compounds VII and VIII, below), and the analogous 1- and 3-acylates are produced, when, alternative acids are used for solvolysis.



VII



VIII

Direct basic hydrolysis of this mixture under standard conditions then produces the desired 1α-hydroxy-19-nor-vitamin D compounds of structure I above (wh re X^1 and X^2 are hydrog n). Alt rnatively, the above mixture of monoacetates or other acylates may also be separated (e.g. by high pressure liquid chromatography) and the resulting 1-acetate and 3-acetate is mers may be subj cted separately to hydrolysis to obtain the same

final product from each, namely the 1α-hydroxy-19-nor-vitamin D compounds of structure I. Also the separated monoacetates of structure VII or VIII or the free 1,3-dihydroxy compound can, of course, be reacylated according to standard procedures with any desired acyl group, so as to produce the product of structure I above, where X^1 and X^2 represent acyl groups which may be the same or different.

Biological Activity of 1α-Hydroxy-19-Nor-Vitamin D Compounds

The novel compounds of this invention exhibit an unexpected pattern of biological activity, namely high potency in promoting the differentiation of malignant cells and little or no activity in calcifying bone tissue. This is illustrated by the biological assay results obtained for 1α,25-dihydroxy-19-nor-vitamin D_3 (compounds Ia), which are summarized in Tables 1 and 2, respectively. Table 1 shows a comparison of the activity of the known active metabolite 1α,25-dihydroxyvitamin D_3 and the 19-nor analog (Ia) in inducing the differentiation of human leukemia cells (HL-60 cells) in culture to normal cells (monocytes). Differentiation activity was assessed by three standard differentiation assays, abbreviated in Table 1 as NBT (nitroblue tetrazolium reduction), NSE (non-specific esterase activity), and PHAGO (phagocytosis activity). The assays were conducted according to known procedures, as given, for example, by DeLuca et al. (U.S. Patent 4,717,721) and Ostrem et al., J. Biol. Chem. 262, 14164, 1987). For each assay, the differentiation activity of the test compounds is expressed in terms of the percent of HL-60 cells having differentiated to normal cells in response to a given concentration of test compound.

The results summarized in Table 1 clearly show that the new analog, 1α,25-dihydroxy-19-nor-vitamin D_3 (Ia) is as potent as 1α,25-dihydroxyvitamin D_3 in promoting the differentiation of leukemia cells. Thus in all three assays close to 90% of the cells are induced to differentiate by 1α,25-dihdyroxyvitamin D_3 at a concentration of 1×10^{-7} molar, and the same degree of differentiation (i.e. 90, 84 and 90%) is achieved by the 19-nor analog (Ia).

Table 1

Differentiation of HL-60 Cells

1α,25-dihydroxyvitamin D_3 (moles/liter)	% Differentiated Cells (mean ± SEM)		
	NBT	NSE	PHAGO
1×10^{-7}	86 ± 2	89 ± 1	87 ± 3
1×10^{-8}	60 ± 2	60 ± 3	64 ± 2
1×10^{-9}	33 ± 2	31 ± 2	34 ± 1
1α,25-Dihydroxy-19-nor-vitamin D_3, (Ia) (moles/liter)			
2×10^{-7}	94 ± 2	95 ± 3	94 ± 2
1×10^{-7}	90 ± 4	84 ± 4	90 ± 4
5×10^{-8}	72 ± 3	73 ± 3	74 ± 3
1×10^{-8}	61 ± 3	60 ± 3	56 ± 1
1×10^{-9}	32 ± 1	31 ± 1	33 ± 1

In contrast to the preceding results, the new 19-nor analog (Ia) xhibits no activity in an assay measuring the calcification of bone, a typical response elicited by vitamin D compounds. Relevant data, representing the

results of an assay comparing the bone calcification activity in rats of 1α,25-dihydroxyvitamin D_3 and 1α,25-dihydroxy-19-nor-vitamin D_3 (Ia), are summarized in Table 2. This assay was conducted according to the procedure described by Tanaka et al., Endocrinology 92, 417 (1973).

Th results pres nted in Table 2 show the expected bone calcification activity of 1α,25-dihydroxyvitamin D_3 as reflected by the increase in p rcent bone ash, and in total ash at all dos levels. In contrast, the 19-nor analog Ia exhibits no activity at all three dose levels, when compared to the vitamin D-deficient (-D) control group.

Table 2

Calcification Activity

Compound	Amount Administered* (pmoles/day/7 days)	% Ash (mean ± SEM)	Total Ash (mg) (mean ± SEM)
-D (control)	0	19 ± 0.8	23 ± 1.2
1α,25-dihydroxy-vitamin D_3	32.5	23 ± 0.5	34 ± 1.6
	65.0	26 ± 0.7	36 ± 1.1
	325.0	28 ± 0.9	40 ± 1.9
1α,25-dihydroxy-19-nor-vitamin D_3 (Ia)	32.5	22 ± 0.9	28 ± 1.6
	65.0	19 ± 1.5	28 ± 3.4
	325.0	19 ± 1.2	30 ± 2.4

* Each assay group comprised 6 rats, receiving the indicated amount of test compound by intraperitoneal injection daily for a period of seven days.

Thus the new 19-nor analog shows a selective activity profile combining high potency in inducing the differentiation of malignant cells with very low or no bone calcification activity. The compounds of this novel structural class, therefore, can be useful as therapeutic agents for the treatment of malignancies. Because the differentiative activity of vitamin D compounds on keratinocytes of skin (Smith et al., J. Invest. Dermatol. 86, 709, 1986; Smith et al., J. Am. Acad. Dermatol. 19, 516, 1988) is believed to be an indication of successful treatment of psoriasis (Takamoto et al., Calc. Tissue Int. 39, 360, 1986), these compounds should prove useful in treating this and other skin disorders characterized by proliferation of undifferentiated skin cells. These compounds should also find use in the suppression of parathyroid tissue, as for example, in cases of secondary hyperparathyroidism found in renal disease (Slatopolsky et al., J. Clin. Invest. 74, 2136, 1984).

For treatment purposes, the novel compounds of this invention can be formulated in a solid or liquid vehicle ingestible by, and non toxic to, mammals,, for example as solutions in innocuous solvents or as emulsions, suspensions or dispersions in suitable innocuous solvents or carriers, or as pills, tablets or capsules, containing solid carriers according to conventional methods known in the art. Accordingly the present invention provides a pharmaceutical composition which comprises at least one compound of this invention tog ther with a pharmaceutically acceptable excipi nt. For topical applications or administrations the compounds are advantageously formulated as creams or ointments or similar vehicle suitable for topical applications. Any such formulations may also contain other pharmaceutically-acceptable and non-toxic excipients such as stabiliz rs, antixidants, bind rs, coloring agents or emulsifying or taste-modifying ag nts.

The compounds are advantage usly administered by injection (for parenteral administration), or by intra-

ven us infusion of suitable sterile solutions, or in th form of oral dos s (f r oral administration) via the alimentary canal, or topically in the form of ointmcnts, lotions, or in suitable transdermal patches. For the treatment of malignant diseases, the 19-nor-vitamin D compounds of this invention should be administered to subj cts in dosages sufficient to inhibit the proliferation of malignant cells and induce their differentiation into normal monocyte-macrophages. Similarly, for the treatment of psoriasis, the compounds may be administered orally or topically in amounts sufficient to arrest the prolif ration of undifferentiat d keratinocytes, and in the treatment of hyperparathyroidism, the compounds should be administered in dosages sufficient to suppress parathyroid activity, so as to achieve parathyroid hormone levels in the normal range. Suitable dosage amounts are from 1 to 500 μg of compound per day, such dosages being adjusted, depending on diseases to be treated, its severity and the response or condition of the subject as well-understood in the art. Typically a composition contains, in a single dosage form, from 0.5 μg to 50 μg of the compound.

This invention is more specifically described by the following illustrative examples. In these examples specific products identified by Roman numerals and letters, i.c. Ia, Ib, ..., IIa, IIb, ..., etc. refer to the specific structures and side chain combinations identified in the preceding description.

Example 1

Preparation of 1α,25-dihydroxy-19-nor-vitamin D_3 (Ia)

(a) 1α,25-Dihydroxy-3,5-cyclovitamin D_3 1-acetate, 6-methyl etherb: Using 25-hydroxyvitamin D_3 (IIa) as starting material, the known 1α,25-dihydroxy-3,5-cyclovitamin D_3 derivative IIIa (X=H) was prepared according to published procedures (DeLuca et al., U.S. Patent 4, 195,027 and Paaren et al., J. Org. Chem. 45, 3252 (1980)). This product was then acetylated under standard conditions to obtain the corresponding 1-acetate derivative IIIa (X=Ac).

(b) 10,19-Dihydro-1α,10,19,25-tetrahydroxy-3,5-cyclovitamin D_3 1-acetate, 6-methyl ether (IVa): Intermediate IIIa (X=Ac) was treated with a slight molar excess of osmium tetroxide in pyridine according to the general procedure described by Paaren et al. (J. Org. Chem. 48, 3819 (1983)) to obtain the 10,19-dihydroxylated derivative IVa. Mass spectrum m/z (relative intensity), 506 (M^+, 1), 488 (2), 474 (40), 425 (45), 396 (15), 285 (5), 229 (30), 133 (45), 59 (80), 43 (100). ^1H NMR ($CDCl_3$) δ 0.52 (3H, s, 18-CH_3), 0.58 (1H, m, 3-H), 0.93 (3H, d, J=6.1 Hz, 21-CH_3), 1.22 (6H, s, 26-CH_3 and 27-CH_3), 2.10 (3H, s, $COCH_3$), 3.25 (3H, s, 6-OCH_3), 3.63 (2H, m, 19-CH_2), 4.60 (1H, d, J=9.2 Hz, 6-H), 4.63 (1H, dd, 1β-H), 4.78 (1H, d, J=9.2 Hz, 7-H).

(c) 1α,25-Dihydroxy-10-oxo-3,5-cyclo-19-nor-vitamin D_3 1-acetate, 6-methyl ether (Va): The 10,19-dihydroxylated intermediate IVa was treated with a solution of sodium metaperiodate according to the procedure given by Paaren et al. (J. Org. Chem. 48, 3819, 1983) to produce the 10-oxo-cyclovitamin D derivative (Va, X=Ac). Mass spectrum m/z (relative intensity) 442 (M^+-MeOH) (18), 424 (8), 382 (15), 364 (35), 253 (55), 225 (25), 197 (53), 155 (85), 137 (100). ^1H NMR ($CDCl_3$) δ 0.58 (3H, s, 18-CH_3), 0.93 (3H, d, J=6.6 Hz, 21-CH_3), 1.22 (6H, s, 26-CH_3 and 27-CH_3), 2.15 (s, 3-$OCOCH_3$), 3.30 (3H, s, 6-OCH_3), 4.61 (1H, d, J=9.1 Hz, 6-H), 4.71 (1H, d, J=9.6 Hz, 7-H), 5.18 (1H, m, 1β-H).

It has been bound also that this diol cleavage reaction does not require elevated temperatures, and it is, indeed, generally prefereable to conduct the reaction at approximately room temperature.

(d) 1α-Acetoxy-10,25-dihydroxy-3,5-cyclo-19-nor-vitamin D_3 6-methyl ether (VIa, X-Ac, Y=OH): The 10-oxo derivative Va (X=Ac) (2.2 mg, 4.6 μmol) was dissolved in 0.5 ml of ethanol and to this solution 50 μl (5.3 μmol) of a $NaBH_4$ solution (prepared from 20 mg of $NaBH_4$, 4.5 ml water and 0.5 ml of 0.01 N NaOH solution) was added and the mixture stirred at 0°C for ca. 1.5 h, and then kept at 0°C for 16 h. To the mixture ether was added and the organic phase washed with brine, dried over $MgSO_4$, filtered and evaporated. The crude product was purified by column chromatography on a 15 x 1 cm silica gel column and the alcohol VIa (X=Ac, Y=OH) was eluted with ethyl acetate hexane mixtures to give 1.4 mg (3 μmol) of product. Mass spectrum m/z (relative intensity) 476 (M^+) (1), 444 (85), 426 (18), 384 (30), 366 (48), 351 (21), 255 (35), 237 (48), 199 (100), 139 (51), 59 (58).

(e) 1α,25-Dihydroxy-19-nor-vitamin D_3(Ia, X^1=X^2=H): The 10-alcohol (VIa, X=Ac, Y=OH) (1.4 mg) was dissolved in 100 μl anhydrous CH_2Cl_2 and 10 μl (14 μmol) triethylamine solution [prepared from 12 mg (16 μl) triethylamine in 100 μl anhydrous CH_2Cl_2], followed by 7 μl (5.6 μmol) mesyl chloride solution (9 mg mesyl chloride, 6.1 μl, in 100 μl anhydrous CH_2Cl_2) added at 0°C. The mixture was stirred at 0°C for 2 h. The solvents were removed with a stream of argon and the residue (comprising compound VIa, X=Ac, Y=CH_3SO_2O-) dissolved in 0.5 ml of anhydrous tetrahydrofuran; 5 mg of $LiAlH_4$ was added at 0°C and the mixtur kept at 0°C for 16 h. Excess $LiAlH_4$ was decompos d with wet ether, the ether phase was washed with water and dried over $MgSO_4$, filtered and evaporated to giv the 19-nor product VIa (X=Y=H).

This product was dissolved in 0.5 ml of acetic acid and stirred at 55°C for 20 min. The mixture was cooled,

ice water added and extracted with ether. Th other phase was washed with cold 10% sodium bicarbonate solution, brine, dried over $MgSO_4$, filtered and evaporated to give the expected mixture of 3-acetoxy-1α-hydroxy- and 1α-acetoxy-3-hydroxy isomers, which were separated and purified by HPLC (Zorbax Sil column, 6.4 x 25 cm, 2-pr panol in h xane) to give about 70 µg each of compounds VIIa and XIIIa. UV (in EtOH) λ_{max} 242.5 (OD 0.72), 251.5 (OD 0.86), 260 (OD 0.57).

Both 19-nor-1,25-dihydroxyvitamin D_3 acetates VIIa and VIIIa were hydrolyzed in the same manner. Each of the monoacetates was dissolved in 0.5 ml of ether and 0.5 ml 0.1 N KOH in methanol was added. The mixture was stirred under argon atmosphere for 2 h. More ether was added and the organic phase washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was dissolved in a 1:1 mixture of 2-propanol and hexane and passed through a Sep Pak column and washed with the same solvent. The solvents were evaporated and the residue purified by HPLC (Zorbax Sil, 6.4 x 25 cm, 10% 2-propanol in hexane). The hydrolysis products of VIIa and VIIIa were identical and gave 66 µg of Ia (X^1=X^2=H). Mass spectrum (m/z relative intensity) 404 (M^+) (100), 386 (41), 371 (20), 275 (53), 245 (51), 180 (43), 135 (72), 133 (72), 95 (82), 59 (18), exact mass calcd. for $C_{26}H_{44}O_3$ 404.3290, found 404.3272. ^{1}H NMR ($CDCl_3$) δ 0.52 (3H, s, 18-CH_3), 0.92 (3H, d, J=6.9 Hz, 21-CH_3), 1.21 (6H, s, 26-CH_3 and 27-CH_3), 4.02 (1H, m, 3α-H), 4.06 (1H, m, 1β-H), 5.83 (1H, d, J=11.6 Hz, 7-H), 6.29 (1H, d, J=10.7 Hz, 6-H). UV (in EtOH), λ_{max} 243 (OD 0.725), 251.5 (OD 0.823), 261 (OD 0.598).

Example 2

Preparation of 1α-hydroxy-19-nor-vitamin D_3 (Ib)

(a) With vitamin D_3 (IIb) as starting material, and utilizing the conditions of Example 1a, there is obtained known 1α-hydroxy-3,5-cyclovitamin D_3 1-acetate, 6-methyl ether, compound IIIb (X=Ac).

(b) By subjecting intermediate IIIb (X=Ac), as obtained in Example 2a above to the conditions of Example 1b, there is obtained 10,19-dihydro-1α,10,19-trihydroxy-3,5-cyclovitamin D_3 1-acetate, 6-methyl ether IVb (X=Ac).

(c) By treatment of intermediate IVb (X=Ac) with sodium metaperiodate according to Example 1c above, there is obtained 1α-hydroxy-10-oxo-3,5-cyclo-19-nor-vitamin D_3 1-acetate, 6-methyl ether Vb (X=Ac).

(d) Upon reduction of the 10-oxo-intermediate Vb (X=Ac) under the conditions of Example 1d above, there is obtained 1α-acetoxy-10-hydroxy-3,5-cyclo-19-nor-vitamin D_3 6-methyl ether VIb (X=Ac, Y=OH).

(e) Upon processing intermediate VIb (X=Ac, Y=OH) through the procedure given in Example 1e above, there is obtained 1α-hydroxy-19-nor-vitamin D_3 (Ib, X^1=X^2=H).

Example 3

Preparation of 1α,25-dihydroxy-19-nor-vitamin D_2

(a) Utilizing 25-hydroxyvitamin D_2 (IIc) as starting material and experimental conditions analogous to those of Example 1a, there is obtained 1α,25-dihydroxy-3,5-cyclovitamin D_2 1-acetate, 6-methyl ether, compound IIIc (X=Ac).

(b) Subjecting intermediate IIId (X=Ac), as obtained in Example 3a above, to the reaction conditions of Example Ib, provides 10,19-dihydro-1α,10,19,25-tetrahydroxy-3,5-cyclovitamin D_2 1-acetate, 6-methyl ether, IVc (X=Ac).

(c) By treatment of intermediate IVc (X=Ac) with sodium metaperiodate according to general procedures of Example 1c above, there is obtained 1α,25-dihydroxy-10-oxo-3,5-cyclo-19-nor-vitamin D_2 1-acetate, 6-methyl ether Vc (X=Ac).

(d) Upon reduction of the 10-oxo-intermediate Vc (X=Ac) under conditions analogous to those of Example 1d above, there is obtained 1α-acetoxy-10,25-dihydroxy-3,5-cyclo-19-nor-vitamin D_2 6-methyl ether VIc (X=Ac, Y=OH).

(e) Upon processing intermediate VIc (X=Ac, Y=OH) through the procedural steps given in Example 1e above, there is obtained 1α,25-dihydroxy-19-nor-vitamin D_2 (Ic, X^1=X^2=H).

Example 4

Preparation of 1α-hydroxy-19-nor-vitamin D_2

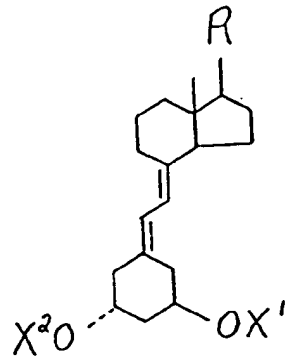
(a) With vitamin D_2 (IId) as starting material, and utilizing the conditions of Example 1a, there is obtained known 1α-hydroxy-3,5-cyclovitamin D_2 1-acetate, 6-m thyl ether, compound IIId (X=Ac).

(b) By subjecting int rmediat IIId (X=Ac), as obtained in Exampl 4a ab v to the conditions of Exampl 1b, there is obtained 10,19-dihydro-1α,10,19-trihydroxy-3,5-cyclovitamin D_2 1-acetate, 6-methyl ether,

IVd (X=Ac).
(c) By treatment of intermediate IVb (X=Ac) with sodium metaperiodate according to Example 1c above, there is obtained 1α-hydroxy-10-oxo-3,5-cyclo-19-nor-vitamin D_2 1-acetat , 6-methyl ether, Vd (X=Ac).
(d) Upon reduction of the 10-oxo-intermediate Vd (X=Ac) under th conditi ns of Example 1d above, there is obtained 1α-acetoxy-10-hydroxy-3,5-cyclo-19-nor-vitamin D_2 6-methyl ther, VId (X=Ac, Y=OH).
(e) Upon processing intermediate VId (X=Ac, Y=OH) through th procedure given in Example 1e above, there is obtained 1α-hydroxy-19-nor-vitamin D_2 (Id, X^1=X^2=H).

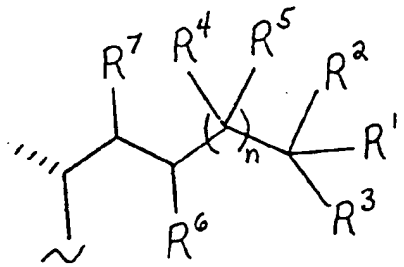
Claims

1. A compound having the formula:



where X^1 and X^2 are each independently hydrogen, aliphatic acyl of 1 to 5 carbon atoms, aromatic acyl or alkylsilyl or alkoxyalkyl wherein said "alkyl" has 1 to 5 carbon atoms, and R is a side chain known for vitamin D-type compounds:

2. A compound according to claim 1 wherein R is hydroxyalkyl of 1 to 5 carbon atoms, fluoroalkyl of 1 to 5 carbon atoms or a side chain of the formula:



wherein R^1 represents hydrogen, hydroxy or O-acyl, R^2 and R^3 are each independently alkyl, hydroxyalkyl or fluoroalkyl, or, when taken together represent the group
-- $(CH_2)_m$ -- where m is an integer from 2 to 5, R^4 is hydrogen, hydroxy, fluorine, O-acyl, alkyl, hydroxyalkyl or fluoroalkyl, R^5 is hydrogen, fluorine, alkyl, hydroxyalkyl or fluoroalkyl, or R^4 and R^5 taken together represent double-bonded oxygen, R^6 and R^7 are each independently hydrogen, hydroxy, O-acyl, fluorine or alkyl, or, R^6 and R^7 taken together form a carbon-carbon double bond, and n is an integer from 1 to 5 and wherein the carbon at any one of positions 20, 22 or 23 in the side chain may be replaced by an O, S, or N atom and wherein said "alkyl" has 1 to 5 carbon atoms and said "acyl" is aliphatic acyl of 1 to 5 carbon atoms or aromatic acyl.

3. A compound according to claim 1 wherein X^1 and X^2 are both hydr gen, R^1 is hydroxy, R^2 and R^3 are ach independently methyl, trifluoromethyl, ethyl or propyl, R^6 and R^7 are both hydrogen, or together form a carbon-carbon double bond, R^4 and R^5 are both hydrogen and n is 1, 2 or 3.

4. 1α,25-Dihydroxy-19-nor-vitamin D_3.

5. 1α-Hydroxy-19-nor-vitamin D_3.

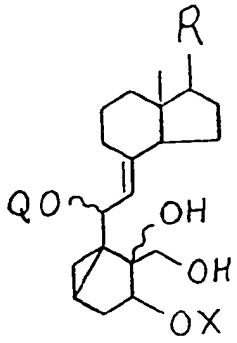
6. 1α,25-Dihydroxy-19-nor-vitamin D_2.

7. 1α-Hydroxy-19-nor-vitamin D_2.

8. 1α-Hydroxy-19-nor-24 epi-vitamin D_2.

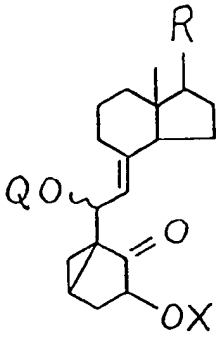
9. 1α,25-Dihydroxy-19-nor-24 epi-vitamin D_2.

10. A compound having the formula:



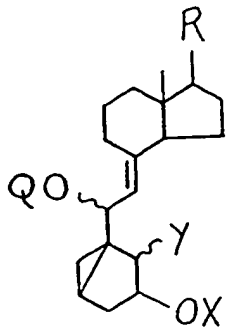
wherein R is as defined in Claim 1, Q represents alkyl and X is hydrogen, acyl, alkylsilyl or alkoxyalkyl, wherein said "alkyl" has 1 to 5 carbon atoms and said "acyl" is aliphatic acyl of 1 to 5 carbon atoms or aromatic acyl.

11. A compound having the formula:



wherein R is as defined in Claim 1, Q represents alkyl of 1 to 5 carbon atoms and X is as defined in Claim 10.

12. A compound having the formula:



wherein R is as defined in Claim 1, Q and X are as defined in claim 10, and Y is hydroxy, hydrogen or protected hydroxy where the protecting group is acyl, alkylsilyl or alkoxyalkyl, wherein said "alkyl" has 1 to 5 carbon atoms and said "acyl" is aliphatic acyl of 1 to 5 carbon atoms or aromatic acyl.

13. A pharmaceutical composition which comprises at least one compound as claimed in any one of claims 1 to 9 together with a pharmaceutically acceptable excipient.

14. A composition according to claim 13 wherein the compound is in a solid or liquid vehicle ingestible by, and non-toxic to, mammals.

15. A composition according to claim 13 or 14 wherein the compound is 1α,25-hydroxy-19-nor-vitamin D_3, 1α-hydroxy-19-nor-vitamin D_3, 1α,25-dihydroxy-19-nor-vitamin D2 or 1α-hydroxy-19-nor-vitamin D_2.

16. A composition according to any one of claims 13 to 15 which contains, in a single dosage form, from 0.5 μg to 50μg of the compound.

17. A composition according to any one of claims 13 to 16 which is suitable for topical administration.

18. A composition according to any one of claims 13 to 16 which is suitable for parenteral administration.

19. A composition according to any one of claims 13 to 16 which is suitable for oral administration.

20. A compound as defined in any one of claims 1 to 9 for inducing cell differentiation in malignant cells.

21. A compound as defined in any one of claims 1 to 9 for inducing cell differentiation in leukemia cells.

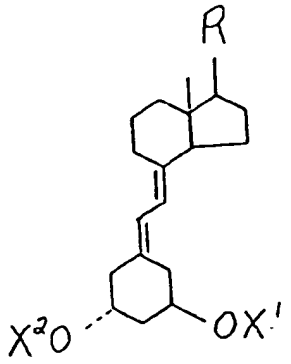
22. A compound as defined in any one of claims 1 to 9 for treating a proliferative skin disorder in a mammal.

23. A compound as defined in any one claims 1 to 9 for treating psoriasis.

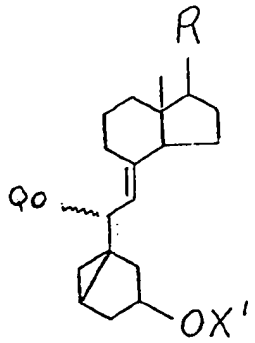
24. A compound as defined in any one of claims 1 to 9 for treating primary or secondary hyperparathyroidism.

25. A compound as defined in any one of claims 1 to 9 for treating a neoplastic disease.

26. A process for preparing a compound having the formula:



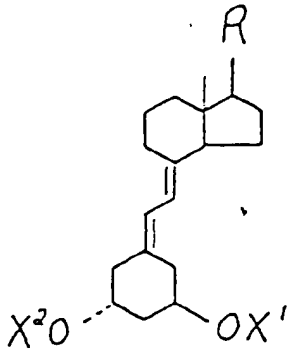
where X^1, X^2 and R are as defined in any one of Claims 1 to 3 which comprises solvolysing the 1α-hydroxy-10-deoxy cyclovitamin D compound having the formula:



wherein Q is alkyl of 1 to 5 carbon atoms.

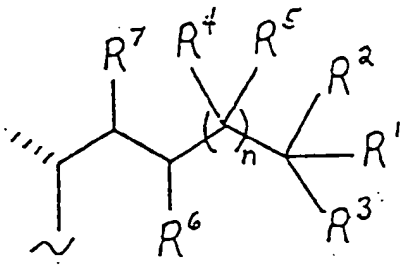
Patentansprüche

1. Verbindung der Formel



worin X1 und X2 unabhängig voneinander Wasserstoff, aliphatisches Acyl mit 1 bis 5 Kohlenstoffatomen, aromatisches Acyl oder Alkylsilyl oder Alkoxyalkyl, worin "Alkyl" 1 bis 5 Kohlenstoffatome besitzt, bedeuten, und R eine für Verbindungen des Vitamin-D-Typs bekannte Seitenkette ist.

2. Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß R Hydroxyalkyl mit 1 bis 5 Kohlenstoffatomen, Flu ralkyl mit 1 bis 5 Kohlenstoffatomen oder in Seitenkette der Formel ist:



worin R1 Wasserstoff, Hydroxy oder O-Acyl bedeutet, R2 und R3 unabhängig voneinander Alkyl, Hydroxyalkyl oder Fluoralkyl bedeuten oder zusammengenommen die Gruppe -- $(CH_2)_m$ -- darstellen, worin m eine ganze Zahl von 2 bis 5, R4 Wasserstoff, Hydroxy, Fluor, O-Acyl, Alkyl, Hydroxyalkyl oder Fluoralkyl ist, R5 Wasserstoff, Fluor, Alkyl, Hydroxyalkyl oder Fluoralkyl ist, oder R4 und R5 zusammen einen doppelt gebundenen Sauerstoff bedeuten, R6 und R7 unabhängig voneinander Wasserstoff, Hydroxy, O-Acyl, Fluor oder Alkyl sind, oder R6 and R7 zusammen eine Kohlenstoff-Kohlenstoff-Doppelbindung bilden, und n eine ganze Zahl von 1 bis 5 ist, und worin das Kohlenstoffatom an irgendeiner der Stellungen 20, 22 oder 23 in der Seitenkette durch ein O, S oder N-Atom ersetzt sein kann, und worin "Alkyl" 1 bis 5 Kohlenstoffatome besitzt, und "Acyl" ein aliphatisches Acyl mit 1 bis 5 Kohlenstoffatomen oder ein aromatisches Acyl ist.

3. Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß X1 und X2 beide Wasserstoff sind, R1 Hydroxy ist, R2 und R3 unabhängig voneinander Methyl, Trifluormethyl, Ethyl oder Propyl bedeuten, R6 und R7 beide Wasserstoff sind, oder zusammen eine Kohlenstoff-Kohlenstoff-Doppelbildung bilden, R4 und R5 beide Wasserstoff sind, und n 1, 2 oder 3 ist.

4. 1α,25-Dihydroxy-19-nor-Vitamin-D3

5. 1α-Hydroxy-19-nor-Vitamin-D3

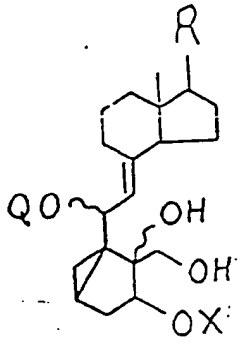
6. 1α,25-Dihydroxy-19-nor-Vitamin-D2

7. 1α-Hydroxy-l9-nor-Vitamin-D2

8. 1α-Hydroxy-19-nor-24 epi-Vitamin-D2

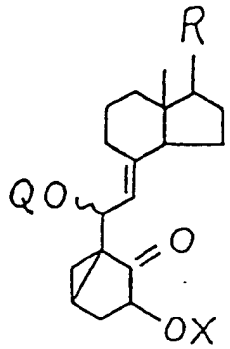
9. 1α,25-Dihydroxy-19-nor-24 epi-Vitamin-D2

10. Verbindung der Formel



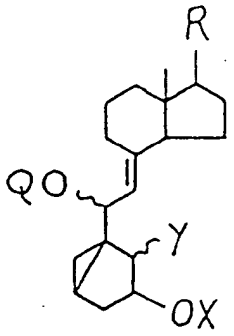
worin R die im Anspruch 1 ang gebene Bedeutung besitzt, Q Alkyl b deutet und X Wasserstoff, Acyl, Alkylsilyl oder Alkoxyalkyl ist, und worin "Alkyl" 1 bis 5 Kohlenstoffatome besitzt, und "Acyl" ein aliphatisches Acyl mit 1 bis 5 Kohlenstoffatomen oder ein aromatisches Acyl ist.

11. Verbindung der Formel:



worin R die im Anspruch 1 angegebene Bedeutung besitzt, Q Alkyl mit 1 bis 5 Kohlenstoffatomen bedeutet, und X die im Anspruch 10 angegebene Bedeutung besitzt.

12. Verbindung der Formel:



worin R die im Anspruch 1 angegebene Bedeutung besitzt, Q und X die im Anspruch 10 angegebene Bedeutung besitzen und Y Hydroxy, Wasserstoff oder eine geschützte Hydroxygruppe ist, worin die Schutzgruppe Acyl, Alkylsilyl oder Alkoxyalkyl ist, und worin "Alkyl" 1 bis 5 Kohlenstoffatome besitzt und "Acyl" ein aliphatisches Acyl mit 1 bis 5 Kohlenstoffatomen oder ein aromatisches Acyl ist.

13. Pharmazeutische Zusammensetzung, dadurch gekennzeichnet, daß sie mindestens eine Verbindung nach einem der Ansprüche 1 bis 9 zusammen mit einem pharmazeutisch annehmbaren Träger umfaßt.

14. Zusammensetzung nach Anspruch 13, dadurch gekennzeichnet, daß die Verbindung in einem festen oder flüssigen Träger, der von Säugern mit der Nahrung aufnehmbar und für sie nicht toxisch ist, vorhanden ist.

15. Zusammensetzung nach Anspruch 13 oder 14, dadurch gekennzeichnet, daß die Verbindung 1α,25-Hydroxy-19-nor-Vitamin-D3, 1α-Hydroxy-19-nor-Vitamin-D3, 1α,25-Dihydroxy-19-nor-Vitamin-D2 oder Iα-Hydroxy-19-nor-Vitamin-D2 ist.

16. Zusammensetzung nach einem der Ansprüche 13 bis 15, dadurch gekennzeichnet, daß sie 0.5 µg bis 50 µg der Verbindung in einer Einzeldosisform enthält.

17. Zusammensetzung nach einem der Ansprüche 13 bis 16, dadurch gekennzeichnet, daß sie für eine topische Verabreichung geeignet ist.

18. Zusammensetzung nach einem der Ansprüche 13 bis 16, dadurch gekennzeichnet, daß sie für eine parenterale Verabreichung ge ign t ist.

19. Zusammensetzung nach einem der Ansprüche 13 bis 16, dadurch gekennzeichnet, daß sie für orale Verabreichung geeignet ist.

20. Verbindung nach einem der Asprüche 1 bis 9 zur Induzierung der Zelldifferenzierung in malignen Zellen.

21. Verbindung nach einem der Ansprüche 1 bis 9 zur Induzierung der Zelldifferenzierung in Leukämiezellen.

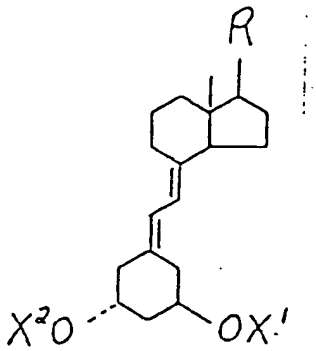
22. Verbindung nach einem der Ansprüche 1 bis 9 zur Behandlung einer sich stark vermehrenden Hautkrankheit in einem Säuger.

23. Verbindung nach einem der Ansprüche 1 bis 9 zur Behandlung von Psoriasis.

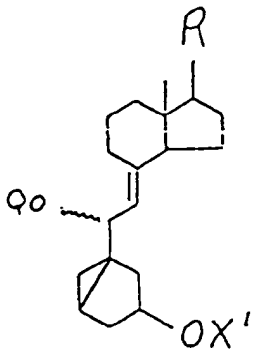
24. Verbindung nach einem der Ansprüche 1 bis 9 zur Behandlung von primärem oder sekundärem Hyperparathyroidismus.

25. Verbindung nach einem der Ansprüche 1 bis 9 zur Behandlung einer neoplastischen Erkrankung.

26. Verfahren zur Herstellung einer Verbindung der Formel:



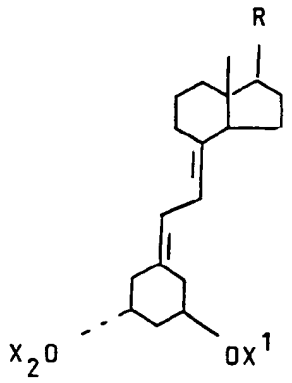
worin X1, X2 und R die in einem der Ansprüche 1 bis 3 angegebene Bedeutung besitzen, dadurch gekennzeichnet, daß man die 1α-Hydroxy-10-deoxy Cyclovitamin-D-Verbindung der Formel:



worin Q Alkyl mit 1 bis 5 Kohlenstoffatomen bedeutet, einer Solvolyse unterwirft.

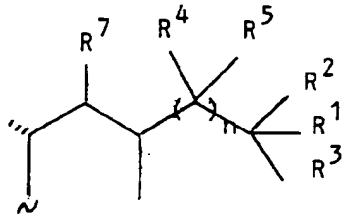
Revendications

1. Composé ayant la formule :



dans laquelle X^1 et X^2 représentent, indépendamment l'un de l'autre, l'hydrogène, un acyle aliphatique ayant 1 à 5 atomes de carbone, un acyle arômatique ou un alkylsilyle ou un alcoxyalkyle dans lequels le radical alkyle a 1 à 5 atomes de carbone, et R est une chaine latérale connue pour les composés du type vitamine D.

2. Composé selon la revendication 1, caractérisé en ce que R représente un radical hydroxyalkyle ayant 1 à 5 atomes de carbone, fluoroalkyle ayant 1 à 5 atomes de carbone ou une chaine latérale de formule :



dans laquelle R^1 représente l'hydrogène, un groupe hydroxy ou O-acyle, R^2 et R^3, indépendamment l'un de l'autre, représentent un radical alkyle, hydroxyalkyle ou fluoroalkyle, ou, pris ensemble, représentent le groupe $-(CH_2)_m-$ où m est un nombre entier de 2 à 5, R^4 représente l'hydrogène, un groupe hydroxy, le fluor, un radical O-acyle, alkyle, hydroxyalkyle ou fluoroalkyle, R^5 représente l'hydrogène, le fluor, un radical alkyle, hydroxyalkyle ou fluoroalkyle, ou R^4 et R^5 pris ensemble représentent une double liaison oxygène, R^6 et R^7 représentent indépendamment l'un de l'autre, l'hydrogène, un groupe hydroxy, le fluor, un radical O-acyle ou alkyle, ou R^6 et R^7 pris ensemble forment une double liaison carbone-carbone, et n est un nombre entier de 1 à 5, et, dans laquelle, le carbone dans l'une quelconque des positions 20, 22 ou 23 de la chaine latérale peut être remplacé par un atome O, S ou N et, dans laquelle, le radical alkyle a 1 à 5 atomes de carbone et le radical acyle est un acyle aliphatique ayant 1 à 5 atomes de carbone ou un acyle arômatique.

3. Composé selon la revendication 1, caractérisé en ce X^1 et x^2 représentent tous deux l'hydrogène, R^1 est un groupe hydroxy, R_2 et R_3 représentent, indépendamment l'un de l'autre, le radical méthyle, trifluorométhyle, éthyle ou propyle, R^6 et R^7 représentent tous deux l'hydrogène, ou forment ensemble une double liaison carbone-carbone, R^4 et R^5 représentent tous deux l'hydrogène et n vaut 1, 2 ou 3.

4. La 1α, 25-Dihydroxy-19-nor-vitamine D_3.

5. La 1α-Hydroxy-19-nor-vitamine D_3.

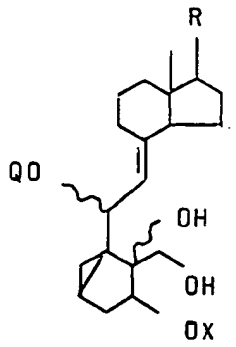
6. La 1α,25-Dihydroxy-19-nor-vitamine D_2.

7. La 1α-Hydroxy-19-nor-vitamin D_2.

8. La 1α-Hydroxy-19-nor-24 epi-vitamine D_2.

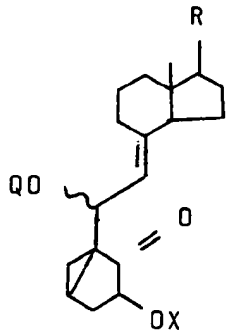
9. La 1α,25-Dihydroxy-19-nor-24 epi-vitamine D_2.

10. Composé ayant la formule :



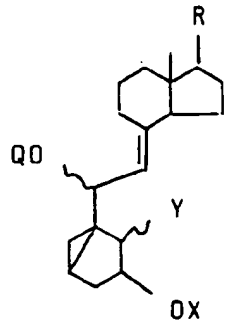
dans laquelle R est tel que défini dans la revendication 1, Q représente un radical alkyle et X représente l'hydrogène, un radical acyle, alkylsilyle ou alcoxyalkyle, dans laquelle ledit radical alkyle a 1 à 5 atomes de carbone et ledit radical acyle est un acyle eliphatique ayant 1 à 5 atomes de carbone ou un acyle aromatique.

11. Composé ayant la formule :



dans laquelle R est tel que défini dans la revendication 1, Q représente un radical alkyle ayant 1 à 5 atomes de carbone et X est tel que défini dans la revendication 10.

12. Composé ayant la formule :



dans laquelle R est tel que défini dans la revendication 1, Q et X sont tels que définis dans la revendication 10, et Y représente un groupe hydroxy, l'hydrogène ou un groupe hydroxy protégé pour lequel le groupement protecteur est un radical acyle, alkylsilyle ou alcoxyalkyle, dans laquelle ledit radical alkyle a 1 à 5 atomes de carbone et ledit radical acyle est un acyle aliphatique ayant 1 à 5 atomes de carbone ou un

acyle arômatique.

13. Composition pharmaceutique qui comprend au moins un composé tel que défini dans l'une quelconque des revendications 1 à 9 ainsi qu'un excipient pharmaceutiquement acceptable.

14. Composition selon la revendication 13, caractérisée en ce que le composé est dans un véhicul solide ou liquide ingérable par et non toxique vis-à-vis des mammifères.

15. Composition selon la revendication 13 ou 14, caractérisée en ce que le composé est la 1α,25-hydroxy-19-nor-vitamine D_3, la 1α-hydroxy-19-nor-vitamine D_3, la 1α,25-dihydroxy-19-nor-vitamine D_2 ou la 1α-hydroxy-19-nor-vitamine D_2.

16. Composition selon l'une quelconque des revendications 13 à 15, caractérisée en ce qu'elle contient, en une seule forme de dosage, 0,5 à 50 µm du composé.

17. Composition selon l'une quelconque des revendications 13 à 16 convenant à l'administration par voie topique.

18. Composition selon l'une quelconque des revendications 13 à 16 convenant à l'administration parentérale.

19. Composition selon l'une quelconque des revendications 13 à 16 convenant à l'administration orale.

20. Composé selon l'une quelconque des revendications 1 à 9 pour provoquer une différenciation cellulaire dans les cellules malignes.

21. Composé selon l'une quelconque des revendications 1 à 9 pour provoquer une différenciation cellulaire dans les cellules de la leucémie.

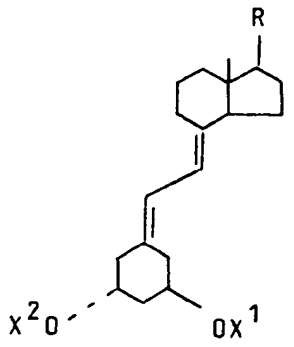
22. Composé selon l'une quelconque des revendications 1 à 9 pour le traitement de maladies prolifératives de la peau chez un mammifère.

23. Composé selon l'une quelconque des revendications 1 à 9 pour le traitement du psoriasis.

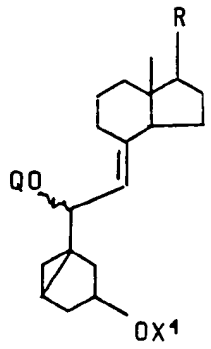
24. Composé selon l'une quelconque des revendications 1 à 9 pour le traitement de l'hyperparathyroïdisme primaire ou secondaire.

25. Composé selon l'une quelconque des revendications 1 à 9 pour le traitement d'une maladie néoplasique.

26. Procédé pour la préparation de composé ayant la formule :



dans laquelle X^1, X^2 et R sont tels que définis dans l'une quelconque des revendications 1 à 3 comprenant la solvolyse du composé 1 -hydroxy-10-déoxy cyclovitamine D ayant la formule :



dans laquelle Q est un radical alkyle ayant 1 à 5 atomes de carbone.